

REMARKS

The Office Action of November 5, 2003 presents the examination of claims 2, 5 and 13, the remaining claims except claim 8 having been withdrawn from consideration. This paper cancels most withdrawn claims and adds new claims 25-32. Claims 2, 5, 8, 13, 23, and 25-32 are pending. Claim 23 presently stands withdrawn.

Claim 8 rejoined

The Examiner indicates that claim 8 has been rejoined to the present application in view of Applicants' arguments presented August 18, 2003. However, claim 8 was not substantially examined, at least no comment upon claim 8 is provided, in the Office Action of November 5, 2003. The Examiner is respectfully requested to substantially examine claim 8 and provide comment in a non-final Office Action.

Claims 23-32 should be presently examined

The Examiner has maintained restriction of claim 23 from the present application. Applicants respectfully request reconsideration of this decision. Claim 23 has been amended to state its minimal components and is presently directed to a kit comprising a protein and a fluorophore, which are the subject matter of composition claims 2, 5, 8 and 13 presently examined,

in separate packages. The Examiner's position that claim 23 represents a separate patentable invention suggests that such a kit is not obvious in view of the composition claim 2.

The claimed kit as described in new claims 25-32 (which recite components previously stated as optional in claim 23) may also comprise packages of materials such as a positive control (a standardized solution of a divalent metal ion), a buffer for maintaining the concentration of free divalent metal ion, and a chelating resin. All of these materials are known in the art and the Examiner's decision not to include them in the present application would constitute a decision that claims 25-32 represent an invention that is not obvious in view of the present claim 2.

The Examiner is respectfully requested to reconsider his prior refusal to include claim 23 (now amended and separated into claims 23 and 25-32) in the present application in view of this clarification of the claims.

Objection to the claims

Claims 2, 5 and 13 were objected to because of the recitation of "7-fluorobenz-2-oxa-1,3-diazole-4-sulfonamide: $\beta$ -mercaptoethanol adduct". The claims have been amended to recite the term "4-(2-hydroxyethylthio)-7-aminosulfonyl-2,1,3-benzoxadiazole". The specification is amended at the first use

of the term "7-fluorobenz-2-oxa-1,3-diazole-4-sulfonamide:β-mercaptopropanol adduct" to include reference to "4-(2-hydroxyethylthio)-7-aminosulfonyl-2,1,3-benzoxadiazole", to provide antecedent basis for that usage in the claims.

Substitute Abstract

A substitute Abstract of less than 150 words has been provided as required by the Examiner.

Incidental amendment of claim 2

Claim 2 is amended to include recitation of 4-aminosulfonyl[1-(4-N-(5-fluoresceinylthioureido)butyl]benzamide. Support for this amendment is provided by the specification at, e.g., page 22, line 15.

Rejections for lack of novelty

Claims 2 and 5 stand rejected under 35 U.S.C. § 102(e) as anticipated by Thompson '517. Claim 5 stands rejected under 35 U.S.C. § 102(b) as anticipated by Thompson et al., *J. Fluorescence* (1992). These rejections are respectfully traversed. Reconsideration and withdrawal thereof are requested.

Claim 2 has been amended to remove the recitation of dansylamide from among the fluorophores of which the composition is comprised. Thus, the instant rejections are overcome.

Rejection for obviousness

Claims 2, 5 and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Thompson '517 or Thompson et al., *J. Fluorescence* (1992), in view of Toyo'oka et al., *Anal. Chem.* (1984). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Toyo'oka et al. is cited for its disclosure of a fluorophore that is a 7-fluorobenz-2-oxa-1,3-diazole-4-sulfonamide: $\beta$ -mercaptoethanol adduct. The Examiner asserts that it would be obvious to substitute the 7-fluorobenz-2-oxa-1,3-diazole-4-sulfonamide: $\beta$ -mercaptoethanol adduct fluorophore for the dansylamide fluorophore of Thompson to obtain the presently claimed invention.

Applicants submit that the Examiner has not properly established *prima facie* obviousness of the claimed invention. While it may be "obvious to try" the substitution suggested by the Examiner, such is not the standard for *prima facie* obviousness.

One element of *prima facie* obviousness is that the substitution must be made with some expectation of success. The

instant application discloses a method for performing divalent metal ion measurement by a fluorescence anisotropy method. A requirement of this method is that the fluorophore have a fairly short fluorescence lifetime. There is no indication given by Toyo'oka that his new fluorophore would have a sufficiently short lifetime to be useful in the fluorescence anisotropy method described in the present application.

Another element of *prima facie* obviousness is that the Examiner must show a motivation, provided either by the references themselves or by the prior art, and not by the present specification, to make the substitution suggested. Applicants submit that the Examiner has not shown such motivation. Indeed, as explained above, the Toyo'oka reference does not disclose the fundamental characteristic, a short fluorescence lifetime, that provides motivation to one of ordinary skill in the art to employ a particular fluorophore in the method disclosed in the present application.

Accordingly, the Examiner's rejection is seen as a hindsight reconstruction of the invention from elements taken from the prior art. That is, the Examiner has found one part of the invention in one reference, another part of the invention in a second reference, and combined the two using the disclosure of the invention in the present application as a template upon which to assemble the references. Such an approach to rejecting

claims has been repeatedly deemed incorrect by the Federal Circuit.

Still further, that the 7-fluorobenz-2-oxa-1,3-diazole-4-sulfonamide: $\beta$ -mercaptoethanol adduct fluorophore can be used in a fluorescence anisotropy method for measuring a divalent metal ion might be seen as a result that would have been unexpected by the skilled artisan who read the Thompson and Toyo'oka references at the time the invention was made. As explained above, there are no characteristics described by Toyo'oka that allow the skilled artisan to predict that 7-fluorobenz-2-oxa-1,3-diazole-4-sulfonamide: $\beta$ -mercaptoethanol adduct could be used with apo-carbonic anhydrase in a fluorescence anisotropy method for measuring divalent metal ions in solution. That such is the case can be seen as an unexpected result sufficient to establish unobviousness of the presently claimed invention.

For all of the above reasons, the instant rejection should be withdrawn. Such favorable action is respectfully requested.

Applicants submit that the present application well describes and claims patentable subject matter. The favorable action of withdrawal of the standing rejections and allowance of the application is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No.

36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for one (1) month extension of time for filing a response in connection with the present application. The required fee of \$55.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: Abstract of the Disclosure